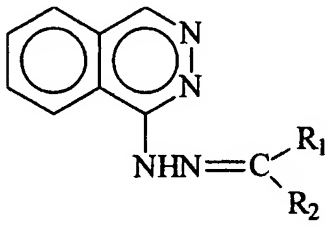
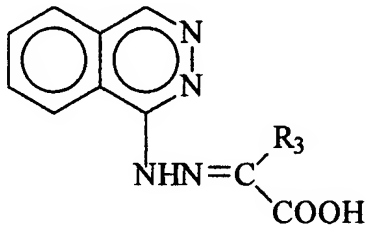
Marked-up version of prior pending Claim 1:

1. (Amended) A method of improving the stability of a hydralazine composition during manufacturing or storage comprising coupling an N-protecting group with hydralazine to produce a compound having the formula:



or a compound having the formula:



where R_1 and R_2 are independently H, substituted or unsubstituted branched or straight chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkylcycloalkyl, lower alkenyl or R_1 and R_2 together form part of a substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon atoms; where R_3 is a branched or straight chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl, [aralkyl,] substituted or unsubstituted alkylcycloalkyl or a group having the formula $(CH_2)_nCOOH$ where n is from 1 to about 7; and

wherein said N-protecting group is labile and is removed from said compound after manufacturing or storage and prior to administration of said compound to a patient.

Please substitute the flowing amended claim for pending Claim 2:

2. (Amended) The method of Claim 1 wherein the N-protecting group is acid-labile and is removed from the hydralazine after storage.

Marked-up version of prior pending Claim 2:

2. (Amended) The method of Claim 1 wherein the N-protecting group is acid-labile and is removed from the hydralazine after storage. [prior to administration of said compound to a patient.]

Please substitute the flowing amended claim for pending Claim 3:

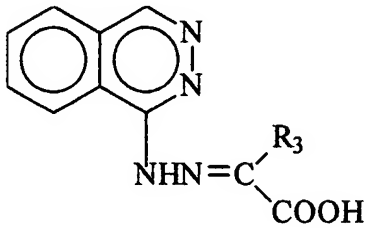
3. (Amended) The method of Claim 2 wherein the hydralazine composition is a sterile injectable solution and the N-protecting group is removed from the hydralazine molecule by adjustment of the pH of said solution.

Marked-up version of prior pending Claim 3:

3. (Amended) The method of Claim 2 wherein the hydralazine composition is a sterile injectable solution and the N-protecting group is [plasma-labile and is] removed from the hydralazine molecule [in plasma after administration of said compound to a patient such that the extent and rate of appearance of hydralazine in the plasma is therapeutically similar to that of hydralazine after administration of hydralazine under similar clinical conditions.] by adjustment of the pH of said solution.

Please substitute the flowing amended claim for pending Claim 10:

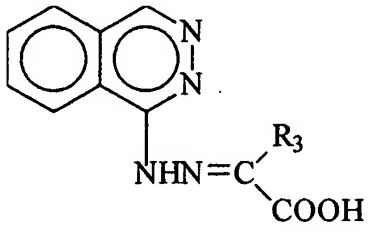
10. (Amended) The method of Claim 1 wherein said compound has the formula:



where R_3 is a branched or straight chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkylcycloalkyl or a group having the formula $(CH_2)_nCOOH$ where n is from 1 to about 7.

Marked-up version of prior pending Claim 10:

10. (Amended) The method of Claim 1 wherein said compound has the formula:



where R_3 is a branched or straight chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl, [aralkyl,] substituted or unsubstituted alkylcycloalkyl or a group having the formula $(CH_2)_nCOOH$ where n is from 1 to about 7.

Please substitute the flowing amended claim for pending Claim 11:

11. (Amended) The method of Claim 10 wherein R_3 is a branched or straight chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkylcycloalkyl.

Marked-up version of prior pending Claim 11:

11. (Amended) The method of Claim 10 wherein R_3 is a branched or straight chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl, [aralkyl,] substituted or unsubstituted alkylcycloalkyl.

Request for Reconsideration and Arguments

In his detailed Office Action, the Examiner rejected Claims 1-7, 10, 11 and 13-19 under 35USC112 as being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention. The Examiner specifically states that the R_3 definition in these claims, the "substituted or unsubstituted aralkyl" and the "aralkyl" groups overlap. Applicant has amended these claims by deleting the overlapping definition "aralkyl" to correct this problem.

In his detailed Office Action, the Examiner rejected Claims 1-20 under 35USC102(b) as anticipated by or, in the alternative, under 35USC103(a) as obvious over Hartmann et al., [Uano] Ueno et al., Wise et al., or any of the Iwaki et al., O'Donnell et al., Lessen et al., Talseth et al. and Druey et al. articles cited in the From PTO-1449. The Examiner specifically states that these prior art references of record all disclose pharmaceutical compositions of hydralazine protected by the N-protecting groups used by the Applicant to improve the stability of a hydralazine pharmaceutical composition. Applicant submits that although these prior art references disclose a few N-protected compounds similar to those claimed by Applicant, these limited number and type of compounds were not used in the same manner as the N-protected compounds disclosed by Applicant to stabilize hydralazine compositions as taught by Applicant. Moreover, there is no suggestion in this prior art to remove the N-protecting group from the hydralazine prior to administration to a patient. Applicant has amended his claims by clearly pointing out that the N-protecting groups are removed from the parent hydralazine compounds prior to administration to a patient. Applicant submits that support for this claim amendment is found on pages 31-32 of the originally filed specification and originally filed Claim 2.

In Claim 1 (Amended), Applicant has now specifically recited that the "N-protecting group is labile and is removed from said compound after manufacturing or storage and prior to administration of said compound to a patient". Applicant submits that none of the prior art references above disclose or suggest a method of improving the stability of a hydralazine composition by first adding the N-protecting groups to hydralazine and secondly removing these groups prior to administration to a patient. Applicant further submits that none of the prior art references of record disclose or suggest any method for stabilizing hydralazine.

In Claim 2 (Amended), Applicant has further recited that the "N-protecting group is acid labile and is removed from the hydralazine after storage". Applicant submits that Claims 3-20 are dependent upon either Amended Claim 1 or Amended Claim 2 are allowable because they incorporate all the limitations and/or changes of the amended Claims 1 and 2.

In Claim 3 (Amended), Applicant has further recited that the hydralazine composition is a sterile injectable solution and the N-protecting group is removed from the hydralazine molecule by adjustment of the pH of said solution.

Applicant submits that hydralazine hydrochloride is very unstable in pharmaceutical formulations currently commercially available. Continuing instability problems with injectable hydralazine hydrochloride, for example, have plagued pharmaceutical manufacturers for many years, forcing these companies to remove their injectable hydralazine products from the marketplace. It is believed that hydralazine hydrochloride undergoes degradation in stored sterile injectable solutions to insoluble polymeric products due to the highly reactive hydrazino group. Hydralazine hydrochloride also undergoes several pharmaceutically undesirable reactions such as chelation with metal ions, oxidation, and pH-dependent decomposition. It is believed that these reactions, which often cause discoloration of hydralazine compositions, are also due to the highly reactive hydrazino group.

In accordance with the presently claimed invention, Applicant has addressed this instability problem by protecting the hydrazino group from unwanted reactions during manufacturing and storage. Claims 1-20 of the present application describe a novel method of improving the stability of hydralazine during manufacturing and storage neither disclosed or suggested by the prior art. Applicant respectfully submits that Claims 1-20 of the present application clearly describe Applicant's solution to this problem, and submits that these claims are now in condition for allowance and request reconsideration for allowance by the Examiner.

Respectfully submitted

Donald L. Barbeau, Inventor
Registration No. 29,766

Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents P.O. Box 1450 Alexandria, VA 22313-1450231 on the date shown below:

Donald L. Barbeau
May 10, 2004